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High dose versus low dose opioid epidural regimens for pain relief in labour (Protocol)

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High dose versus low dose opioid epidural regimens for pain relief in labour

Susan Jordan¹, Fiona A Murphy², Clare Boucher³, Stuart Davies⁴, Amy Brown⁵, Alan Watkins⁶, Lucy J de Lloyd⁷, Margery Morgan⁸, Gareth Morgan⁹

¹Department of Nursing, College of Human & Health Sciences, Swansea University, Swansea, UK. ²Department of Nursing and Midwifery, Faculty of Education and Health Sciences, University of Limerick, Limerick, Ireland. ³ISS, Swansea University, Swansea, UK. ⁴Department of Anaesthetics, Abertawe Bro Morgannwg University Health Board, Swansea, UK. ⁵Department of Public Health and Policy Studies, College of Human & Health Sciences, Swansea University, Swansea, UK. ⁶College of Medicine, Swansea University, Swansea, UK. ⁷Department of Anaesthetics, Cardiff and Vale UHB, Heath Hospital, Cardiff, UK. ⁸Department of Obstetrics, Singleton Hospital, Swansea, UK. ⁹The Children's Trust, Tadworth, UK

Contact address: Susan Jordan, Department of Nursing, College of Human & Health Sciences, Swansea University, Singleton Park, Swansea, SA2 8PP, UK. s.e.jordan@swansea.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To compare the effects (see outcomes below) of different total* doses (in terms of boluses, concentration, volume and timeframe) of opioid epidural (excluding combined-spinal epidural and intrathecal) analgesia administered (alone or as adjunctive) during labour on the woman and the infant.

2. To compare the safety (see outcomes below) of different total* doses (as above) of opioid epidural analgesia administered during labour for the woman and the infant.

*We define 'total' as the sum of all boluses and infusions (concentration, volume and timeframe) administered between onset of labour (as defined by authors) and delivery. If analgesia post-delivery is reported, we shall describe this separately.

We shall undertake secondary analyses of drug concentrations and volumes, see [Types of interventions](#). However, since opioids pass into the fetus, and may accumulate, total dose is an important consideration for infant adverse events, such as drowsiness. (see [Why it is important to do this review](#)).

Description of the condition

BACKGROUND

Pain in labour

The pain experienced in labour is affected by multiple physiological and psychosocial factors (Jones 2012). Perceptions of pain intensity vary. Occasionally women feel no pain in labour. At the other extreme, labour pain has been reported to be the most severe pain that a woman experiences in her lifetime (Melzack 1984).

Physiology

Pain originates from different sites during labour and birth. In the first stage of labour (defined as the period from the onset of labour to the complete dilatation of the cervix) (NLM 1991), pain occurs during contractions, is visceral or cramp-like in nature, originates in the uterus and cervix, and is produced by distension of uterine tissues and dilation of the cervix. In the first stage, pain is transmitted via spinal nerves T10-L1. Labour pain can be referred to the abdominal wall, lumbosacral region, iliac crests, gluteal areas, and thighs. The transition phase of labour refers to the shift from the late first stage (7 cm to 10 cm cervical dilation) to the second stage of labour (full dilation). In the second stage of labour (defined as from full cervical dilation to the delivery of the baby) (Marcovitch 2010), pain occurs from distension of the vagina, perineum, and pelvic floor. In the second stage, pain is transmitted via the pudendal nerves, entering the spinal cord via nerve roots S2-S4. Stretching of the pelvic ligaments is the hallmark of the second stage of labour. Second stage pain is characterised by a combination of visceral pain from uterine contractions and cervical stretching and somatic pain from distension of vaginal and perineal tissues (Jones 2012).

Factors affecting pain in labour

Many factors influence the physiological and psychological processes of birth and the extent to which women experience pain, including parity, induction of labour and the way labour is managed. The pattern of pain appears to differ between nulliparous and multiparous women. Typically, nulliparous women experience greater sensory pain than multiparous women during early labour (before 5 cm dilatation) (Lowe 2002). Women may also experience induced labour as being more painful than spontaneous labour (NCC 2008). The perception of pain and administration of analgesia during childbirth is also influenced by provision of continuous intrapartum support, continuity of care or midwife-led care (Begley 2009; Hodnett 2013; Sandall 2013; Skibsted 1992).

Description of the intervention

Most labouring women require pain relief. Many non-pharmacological methods are helpful, but are often insufficient. The need for effective analgesia in labour has led to widespread adoption of regional or neuraxial analgesia, which may be administered by one of three techniques: epidural, intrathecal, and the combined

spinal-epidural approach. Of these, the epidural route is the most established (NCC 2007).

Epidurals

Epidural analgesia is widely used during labour. Data from the National (UK) Obstetric Anaesthesia Database (NOAD) for 2011 (most recent data available) indicate that 22.7% (126,749/558,256) of women in labour used regional analgesia; this proportion has remained largely unchanged since 2008. In over 91% of these 126,749 women, analgesia was initiated epidurally, with other methods, such as combined spinal epidural anaesthetics, accounting for the remainder (NOAD 2013). *Hospital Episode Statistics 2013* for England 2011/12 suggest similar figures: 99,379 of 668,936 (17.1%) women giving birth received epidural or caudal analgesia without intrathecal analgesia. Use is higher in North America, with 61% of 1,829,302 women who had a singleton birth in a vaginal delivery in 27 states of the USA and Canada in 2008 receiving epidural or spinal anaesthesia (Osterman 2011). Despite widespread adoption of epidural analgesia, successive UK guidelines for intrapartum care highlighted the paucity of the evidence base for optimising epidural regimens (NCC 2007, NCC 2014). Dose optimisation involves evaluating the balance of benefits and harms for the whole dyad, during labour and in the longer term, based on research evidence and shared decision-making between women and healthcare professionals.

Epidural administration involves the injection of drugs, usually both a local anaesthetic and an opioid, into the epidural space in the lower region of the spine, close to the nerves that transmit painful stimuli from the contracting uterus and the birth canal (Jones 2012). The drugs act locally, but also pass into the circulation and cross the placenta (Jordan 2010). The most commonly prescribed local anaesthetic is bupivacaine; levobupivacaine, ropivacaine, and lidocaine/lignocaine are also used in epidural injections (Hillyard 2011). The most commonly prescribed opioid is fentanyl (NCC 2014), but other opioids are used, including morphine, diamorphine, and sufentanil. This review focuses on opioids.

How the intervention might work

The term 'opioid' describes any preparation acting on the body's opioid receptors, for example morphine, diamorphine, fentanyl, and alfentanil. Opioids are chemically related to the body's endorphins and enkephalins, which are natural mood changers and analgesics, particularly in times of pain and stress (Jordan 2010; Vuong 2010).

Opioids act on specific receptors in the central nervous system and throughout the body. This triggers changes within nerve or smooth muscle cells, usually inhibiting their activity and neurotransmitter release. In general, opioids (endogenous and pharmacological) depress the activity of target tissues and have a calming

effect. Opioids attenuate a) the stress response by reducing the activity of the sympathetic nervous system and ACTH secretion (Drolet 2001; Vuong 2010), and b) pain by stimulating opioid receptors in the dorsal horn of the spinal cord, the brain stem (both the reticular activating system and the periaqueductal grey matter), and parts of the frontal cortex (Melzack 1965; Wagner 2007). They also reduce pain transmission in peripheral tissues, particularly where inflammation is present (Carr 1999).

The literature offers no definitions of high and low doses for epidural opioids, and several doses have been compared (see [Types of interventions](#)). The report from a six-arm trial of different dose combinations (fentanyl and ropivacaine) administered in labour, in which there was no follow through by the investigators to the birth, suggested that analgesia using fentanyl plus ropivacaine is determined by the mass of drug administered, rather than concentration or volume (Bernard 2003). In contrast, work on epidural local anaesthetics suggests that analgesia depends on both volume and mass of drug administered, and larger volumes are better able to cover the drug target sites (the nerve roots in the epidural space) (Christiaens 1998; Lyons 2007). However, opioids act on more closely defined targets, receptors on cell bodies in the dorsal horn of the spinal cord (Eltzschig 2003), and may be less reliant on diffusion within the epidural space.

Why it is important to do this review

Consumers identified pain relief in labour as the topic of most importance to them (Jones 2012). However, the overview of systematic reviews of pain management in labour identified no systematic reviews comparing epidural opioid regimens. The only existing systematic review of regimens included in the overview compares bupivacaine with ropivacaine (Halpern 2003). Low concentrations of bupivacaine and fentanyl are recommended for epidural administration (NCC 2014). There is a consensus on the need to use lower concentrations of local anaesthetics (NCC 2014), due, in part, to associations with increased rates of instrumental delivery and difficulty in mobilisation during labour (COMET 2001). However, there is more uncertainty and variation surrounding the appropriate dose of epidural opioids. Although only small quantities of drug reach the maternal and fetal circulations following epidural administration (Eltzschig 2003), there are some concerns about the adverse effects of opioids (Jones 2012; Jordan 2005). Possible maternal adverse effects include: sedation, hypoventilation, hypotension, prolonged labour, urine retention, itching, nausea and/or vomiting, and the slowing of gastric emptying (Jordan 2010). Sedation was less common in women receiving lower doses of sufentanil in combined spinal epidural regimens in a small trial (n = 42) (Sia 1999). If a woman feels drowsy or sedated, she is less likely to mobilise and adopt an upright position and, as a result, this may lengthen her labour and make it more painful (Lawrence 2009).

Opioids readily cross the placenta by passive diffusion: the concentration of fentanyl in the umbilical artery is 89% to 94% of that of maternal venous plasma (Bader 1995; Moises 2005). Fentanyl accumulates in the placental intervillous space (de Barros Duarte 2009) and the fetus (Desprats 1991; Lofuts 1995), and is released from binding proteins (albumins) in the first few hours of neonatal life (Porter 1998). Therefore, the total dose that may be sequestered in placental or fetal tissues merits consideration (Jordan 2005). The fetus has a higher concentration of free or unbound opioids than the mother, and this increases if the fetus becomes acidotic (Helbo-Hansen 1995), for example, in events leading up to emergency caesarean sections. Neonatal respiratory depression and hypothermia are occasionally reported in association with epidural opioids (Carrie 1981), particularly at higher doses (Kumar 2003). Some trials and observational studies suggest associations between epidural analgesia or higher doses of epidural opioids and reduced suckling or breastfeeding rates (Beilin 2005; Henderson 2003; Jordan 2005; Jordan 2009; Torvaldsen 2006). Epidural solutions are administered by bolus or continuous infusion or patient-controlled pump (NCC 2014). Boluses of higher concentrations of local anaesthetics, as used in earlier years, have been associated with a dense motor block resulting in reduced mobility, decreased pelvic tone and impairment of the bearing down effort in the second stage of labour (Thornton 2001). More recently, there has been a trend to use a lower concentration of local anaesthetic in combination with a variety of opioids; these combinations provide analgesia while allowing the woman to maintain some motor function, including the ability to move and bear down during labour (COMET 2001; Russell 2000). As local anaesthetic concentrations have been reduced, opioids have been increased to ensure adequate analgesia, but the dose ranges employed have not, as yet, been subject to the same scrutiny. The most pressing uncertainties include the following.

Instrumental delivery rates

Previous Cochrane reviews have indicated that, when compared with non-epidural analgesia, epidural analgesia increases the rate of instrumental deliveries, while reducing pain during the second stage (Anim-Somuah 2011). How these benefits and harms are mitigated by alterations in dose is uncertain. For example, there is evidence, from nulliparae, that instrumental deliveries are less frequent with lower-dose local anaesthetic regimens (COMET 2001), while a trial of patient-controlled epidural analgesia, in which the doses of fentanyl and ropivacaine were increased in tandem, suggests that instrumental deliveries may be less frequent when smaller, less frequent boluses are available (Lim 2008).

Oxytocin administration

Endogenous and epidural opioids decrease release of oxytocin from the posterior pituitary and reduce contractility of uterine smooth

muscle by direct action on μ_2/μ_2 opioid receptors (Carter 2003; Rahm 2002). Both intravenous opioids (Sosa 2006) and epidurals (Anim-Somuah 2011), increase the need for oxytocin administration. Oxytocin administration is, in turn, associated with a range of adverse effects, including excessive, and extremely painful, uterine contractions (Bramadat 1994; Fraser 1998), escalating the need for analgesia. Its extensive use in women labouring for the first time is of concern (NCC 2007).

Caesarean rates

The impact of epidural analgesia on caesarean section rates merits further analysis. Previous Cochrane reviews have indicated that, when compared with non-epidural analgesia, epidural analgesia increases the rate of caesareans for fetal distress, but not overall, and without adversely affecting Apgar scores (Anim-Somuah 2011). Trials suggest that the incidence of caesarean section is increased if:

1. two or more rescue bolus doses of bupivacaine are administered (Hess 2000);
2. epidural analgesia is administered prior to either cervical dilatation greater than 5 cm (Thorp 1993) or engagement of the fetal head (Traynor 2000), but more recent evidence does not support this (NCC 2014);
3. oxytocin is administered as low dose, rather than high dose (4 to 12 milliunits per minute), regimens (Kotaska 2006);
4. only sections for fetal distress are considered (Anim-Somuah 2011).

These effects have been attributed to the local anaesthetics in the regimens administered, but further investigation is needed.

Infant feeding and neonatal respiratory distress

There is uncertainty regarding the impact of epidural opioids on breastfeeding rates. While some trials have shown an association between higher doses of epidural fentanyl (Beilin 2005, see [Types of interventions](#)) or any epidural fentanyl (Henderson 2003) and feeding infant formula, others found that adding fentanyl to unspecified quantities of bupivacaine (Wilson 2010, see [Types of interventions](#)) and 50 mcg bolus plus infusions, compared with no analgesia during labour (Radzyminski 2003) do not reduce breastfeeding. Despite reassuring findings from a small trial of epidural analgesia with and without fentanyl ($n = 138$) (Porter 1998), a case control study ($n = 412$) found an association between epidurals containing opioids and neonatal respiratory distress (Kumar 2014), and a meta-analysis suggested a higher risk with sufentanil (Li 2015). Accordingly, obstetricians are advised to avoid high doses of opioids before delivery 'for the sake of the infant' (Reynolds 2010; Reynolds 2011).

Floor and ceiling effects

It is possible that different doses above or below certain thresholds will not affect outcomes - the ceiling and floor effects. For example, 95% of women receiving a bolus dose of 50 mcg fentanyl or 8 mcg sufentanil will be pain free for 100 to 180 minutes, based on the empirically derived ED_{95} (Herman 1998). ED_{95} (effective dose for 95%) is the amount of drug needed to achieve the desired effect, or success, in 95% of those exposed. Women receiving 0 to 50 mcg fentanyl bolus experienced less satisfaction and pruritus than those receiving higher doses, but there were minimal differences in outcomes between the 75 and 100 mcg fentanyl groups (Bang 2012).

The transfer of drug into the fetus may vary at different doses. Due to local binding in maternal tissues, the minimum dose to affect the infant may be higher than that affecting the mother, but more evidence is required (Reynolds 2011).

Epidural analgesia is effective (Anim-Somuah 2011). Reduction in pain-induced physiological disturbance is likely to benefit both the woman and the infant (Jordan 2010). Therefore, dose optimisation warrants full investigation. In this systematic review, we compare high- and low-dose epidural regimens, aimed at relieving pain and helping women cope with pain in labour (NCC 2014). Total dose may be a useful marker to identify dyads at risk of adverse events and target extra support (Jordan 2005; Jordan 2009). The clinical relevance of the review will be increased by comparing the concentrations of opioids in the epidural regimen.

OBJECTIVES

1. To compare the effects (see outcomes below) of different total* doses (in terms of boluses, concentration, volume and timeframe) of opioid epidural (excluding combined-spinal epidural and intrathecal) analgesia administered (alone or as adjunctive) during labour on the woman and the infant.

2. To compare the safety (see outcomes below) of different total* doses (as above) of opioid epidural analgesia administered during labour for the woman and the infant.

*We define 'total' as the sum of all boluses and infusions (concentration, volume and timeframe) administered between onset of labour (as defined by authors) and delivery. If analgesia post-delivery is reported, we shall describe this separately.

We shall undertake secondary analyses of drug concentrations and volumes, see [Types of interventions](#). However, since opioids pass into the fetus, and may accumulate, total dose is an important consideration for infant adverse events, such as drowsiness. (see [Why it is important to do this review](#)).

METHODS

Criteria for considering studies for this review

Types of studies

Types of studies to be considered for review will be all parallel-arm randomised controlled trials involving comparison of high and low (but > 0) total doses of epidural opioids administered for pain relief in labour.

We shall include: trials where women are randomised to different doses of the same opioid; unpublished studies, where information can be obtained; multi-arm trials where two or more of the arms compare different doses of epidural opioids*; cluster-randomised trials; unblinded trials. We shall include trials where neither primary nor secondary outcomes are available, and note that they did not contribute data to the review. We shall not restrict by duration of follow up after childbirth.

We shall exclude: trials where women are randomised to different opioids; all quasi-randomised studies; trials where the interventions of interest cannot be separated from co-interventions*; trials reported only in abstract, as they will not include sufficient information (below); trials not following parturients to delivery**. We consider cross-over designs to be inappropriate for evaluation of rapidly evolving situations, such as childbirth.

*Trials where doses of more than one medicine vary between arms. If any trial arms keep the non-opioid dose constant, the study will be included. If both the opioid and the second drug vary, or there is no information on the dose administered, the study will be excluded from the main analysis, as it will be difficult to disentangle the relative contributions.

** Trials that investigate the use of different doses of pain relief, but do not follow the woman through to the birth, will not enable estimation of the total dose administered and therefore will not allow for evaluation of safety outcomes for the mother or infant.

Types of participants

Pregnant women receiving epidural pain relief in labour, regardless of parity and whether labour was spontaneous or induced. (We shall exclude trials (or trial arms): involving women undergoing elective caesareans, recruiting multiple births only, or involving women with known *intrauterine* deaths.) Any trials examining only multiple births or only women with known *intrauterine* deaths will be excluded from the analysis, and reported narratively; it does not seem logical to combine these with trials of singletons.

Types of interventions

High doses versus low doses of opioid epidural analgesia. We shall take two approaches to this.

1. 'High' and 'low' doses of the same opioid, as defined and reported by authors. Information on drug dose will include total dose, boluses, concentration, volume and timeframe. This will

be converted to total dose (drug mass) where possible. It may be necessary to calculate doses from information given and to check these with authors. Where drug concentrations differ, we shall consider the volume administered in a secondary analysis. If any total dose has been administered in different volumes, we shall use this information in this secondary analysis. Some investigators suggest that epidural local anaesthetics are more effective when administered in higher volumes (Lyons 2007), and opioids may act similarly.

2. **Defined doses for selected opioids.** Fentanyl is the most widely reported opioid. Since there is no single threshold available from the literature, it would be appropriate to explore the data based on a series of drug mass aliquots as cut points: 50 mcg, 100 mcg, 150 mcg, 200 mcg, 300 mcg, based on previous randomised studies (that would not meet the criteria for inclusion in this review).

Retrospective analysis of the COMET trial (Wilson 2010) investigated 100 mcg, 200 mcg and 300 mcg total fentanyl doses across three trial arms and non-randomised comparators. The Comet trial was designed to investigate three different techniques for administering local anaesthetics: epidural bolus only, combined spinal epidural, and low-dose epidural infusion. Additional analgesia, both fentanyl and local anaesthetic, were given on request in all arms, but total local anaesthetic doses are not documented (COMET 2001).

Differences in fentanyl's analgesic efficacy were identified between 50 mcg and 100 mcg, but not between 75 mcg and 100 mcg (Bang 2012; Siddik-Sayyid 2008). Neither of these reported on the total dose of local anaesthetic administered in labour.

Beilin 2005 defined high- and low-dose fentanyl as drug mass above and below 150 mcg, as total dose in labour. There is no information on doses of local anaesthetic administered, and some parturients in the zero dose arm received fentanyl.

To increase clinical relevance and improve interpretation, we shall repeat this analysis:

- using different infusion concentrations, for example, 1, 2, 3, 4 mcg/mL of fentanyl, as a secondary analysis.
- including trials where doses of non-opioid analgesia differed between arms or information on supplementary or rescue analgesia is incomplete, as a secondary analysis.

These analyses will be interpreted cautiously; however, they will inform clinicians of the effects of planning opioid analgesia at different doses.

Where there is more than one arm with different doses of the same opioid and a non-opioid arm, we shall include the non-opioid arm in the descriptive analysis only, if appropriate.

Cochrane reviews already cover: *Epidural versus combined spinal epidural analgesia* (Simmons 2012) and *Epidural versus non-epidural or no analgesia in labour* (Anim-Somuah 2011).

Types of outcome measures

This list of outcomes was developed in collaboration with members of the Pregnancy and Childbirth Group (PCG) consumers' group - see 'History' in (Jones 2012). Some additions have been made, pertinent to this review. Should multiple testing be necessary, statistical significance will be interpreted cautiously.

Primary outcomes

Effects of interventions

- Pain intensity and/or satisfaction with pain relief (as defined by authors). Visual analogue scales are widely used.

Safety of interventions

Outcome affecting both mother and baby

- Breastfeeding exclusive* or full** or partial*** (time points specified by authors)
- Method of delivery (unassisted vaginal birth, assisted vaginal birth, caesarean section)

Adverse effects for mother

Based on Anim-Somuah 2011[†]. We shall report all adverse events, including those identified in the literature.

- Nausea and/or vomiting
- Itching
- Drowsiness
- Respiratory depression requiring oxygen administration or other intervention
- Urinary retention
- Maternal hypotension (as defined by authors)/administration of ephedrine
- Headache
- Headache requiring blood patch
- Epidural failure
- Epidural re-siting
- Malposition (as defined by authors)
- Perineal trauma requiring suturing
- Fever
- Shivering/inability to hold infant
- Maternal blood loss (as reported by authors)
- Uterine rupture
- Venous thromboembolic events
- Postnatal depression (authors' definition, treatment for depression or self-reported)
- Long-term backache (as defined by trial authors)

- Other adverse effects or morbidity (e.g. catheterisation during labour, surgical amniotomy, motor blockade, local anaesthetic toxicity, impaired consciousness, meningitis, intensive care unit admission, paralysis, maternal death)

Adverse effects for infant

Based on Anim-Somuah 2011[†].

- Acidosis as defined by cord blood arterial pH less than 7.15
- Apgar score less than seven at five minutes
- Naloxone administration
- Neonatal hypoglycaemia (less than or equal to 1.67 mmol/L)
- Birth trauma (defined by authors)
- Meconium staining of liquor (as reported by authors)
- Admission to special care baby unit/neonatal intensive care unit (as defined by authors)
- Other short-term problems (as defined by authors, e.g. seizures)
- Long-term adverse outcomes of neonatal complications (defined by authors)
- Poor infant outcomes at long-term follow-up (as defined by authors e.g. disability, brachial plexus damage, seizures)
- Other adverse effects as reported by authors (e.g. fetal or neonatal death)

*Exclusive breastfeeding is defined as no other intake, including liquids, water and solids entering the infant's mouth (Bolling 2007; Lobbok 1990). However, WHO (WHO 2008; WHO 2009) relax this to allow 'oral rehydration solution, drops or syrups consisting of vitamins, minerals supplements or medicines' (p.4, p.4, respectively). We propose to use the latter definition.

**Full breastfeeding comprises exclusive breastfeeding (above) plus 'almost exclusive' breastfeeding. The latter includes infants receiving water or juice or ritualistic feeds infrequently, in addition to vitamins or minerals, as long as the vast majority of feeds are breastfeeds (Chantry 2006; Lobbok 1990; WHO 2009). Administration of water is an important consideration for those assessing infantile diarrhoea. Predominant breastfeeding is similar to 'almost exclusive' above, in that only non-human milk and food-based fluids are excluded (WHO 2008).

***Partial breastfeeding is any breastfeeding, even if extensively supplemented by non-human milk or formula feeds (Bolling 2007). Some authors have subdivided this category into high, medium and low (Lobbok 1990). WHO 2008 prefer the term 'complementary feeding'.

†Some of these outcomes are normally associated with the local anaesthetic components of epidural analgesia. We have decided to retain the existing list both to ensure comparability between reviews and lest any reductions in opioid doses are associated with increased local anaesthetic adverse effects.

Secondary outcomes

- Sense of control in labour (as defined by authors)
- Satisfaction with childbirth experience (as defined by authors)
- Additional analgesia/ anaesthesia administered (e.g. total dose and concentration of local anaesthetic administered, number of 'top up' doses administered)
- Numbers receiving uterotonics for augmentation of labour
- Length of first stage of labour
- Length of second stage of labour
- Time between randomisation and delivery
- Caesarean section for fetal distress
- Caesarean section for dystocia
- Complications of mode of delivery, e.g. damage to perineum from instrumental delivery
- Cost (as defined by authors)
- Other outcomes, such as effect (positive or negative) on mother/baby interaction, concentration of drugs in cord blood

Post-delivery and post-operative analgesia may impact on long-term outcomes. All available information will be included and authors contacted if necessary.

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search

Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we plan to search: PubMed (1946 to current); SCOPUS [Elsevier] (primarily 1960 to current); Web of Science [Thomson Reuters] (Citation databases: 1970 to present and Conference Proceedings from 1990 to present); the Maternity & Infant Care Database [OVID] (1971 to current); and CINAHL [Ebsco] (1982 to current). Search strategies to be used for each database are given in [Appendix 1](#).

We also plan to search clinical trials databases identified for planned, ongoing or unpublished trials ([van Enst 2012](#)) ([ClinicalTrials.gov](#), [ISRCTN Registry](#), WHO International Clinical Trials Registry Platform ([ICTRP](#)), International Federation of Pharmaceutical Manufacturers and Associations [[IFPMA](#)]). The search terms we plan to use are given in [Appendix 2](#).

Searching other resources

We shall undertake:

1. handsearches of reference lists of papers identified;
2. searches for full papers relating to abstracts identified.

We will not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Two review authors (from Sue Jordan (SJ), Lucy de Lloyd (LdeL), Fiona Murphy (FM), Amy Brown (AB)) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. All titles and abstracts will be double checked. Where we are uncertain, we shall send for the study. We will resolve any disagreements and uncertainties through discussion or, if required, we will consult the relevant clinical specialists on the team.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. We will enter data into Review Manager software ([RevMan 2014](#)) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (from SJ, FM, AB, LdeL, at least one will have experience of Cochrane reviews or clinical trials, SJ, FM) will

independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements and uncertainties by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias, for example, where information is missing.

We do not plan to include quasi-randomised trials.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

We do not plan to include quasi-randomised trials.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. (For example, anaesthetists administering epidurals will be aware of the doses, but if they take no further part in the trial, this is unlikely to affect outcomes.) We will assess blinding for different outcomes or classes of outcomes separately. Some outcomes, such as pain scores and satisfaction, are subjective, and may be influenced by blinding. Other outcomes, such as method of delivery, are less vulnerable to subjective judgements.

We will assess the methods as:

- low, high or unclear risk of bias for participants;

- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for data analysts.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. For some outcomes, blinding is unlikely to affect the results, for example, caesarean section, forceps delivery. Subjective outcomes, such as pain scores and satisfaction, are more likely to be influenced by blinding.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we shall re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (no or less than 20% missing outcome data AND missing outcome data balanced across groups);
- high risk of bias ($\geq 20\%$ missing outcome data; numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation; denominators unclear or not reported);
- unclear risk of bias.

Where trials report *per protocol* and intention-to-treat analyses, we shall undertake sensitivity analyses.

We shall treat imputed or last observation carried forward data as missing (Moore 2012).

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes [identified on trial registries] and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

We shall tabulate missing outcomes in each study. Reasons for selective reporting will be included, if available. We will contact trial authors for information, if appropriate.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias, for example:

- Imbalance between trial arms in analgesia before labour or after delivery;
- Imbalance between trial arms in non-opioid analgesia during labour.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

We shall report length of time between consent and labour or delivery and duration of follow-up in each study, as markers of study quality.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see *Sensitivity analysis*.

If significant differences between trial arms are found, we shall calculate the number of patients needed in studies with a risk ratio of one to change the number needed to treat (reciprocal of absolute risk reduction) to include 0 in its 95% confidence intervals.

Assessing the quality of the body of evidence using the GRADE approach

The quality of the evidence will be assessed using the GRADE approach as outlined in the *GRADE handbook* in order to assess the quality of the body of evidence relating to the following outcomes. We have selected up to a maximum of seven outcomes for the mother and seven for the infant/offspring covering both short-

and long-term outcomes for the main comparisons (high *versus* low dose [as defined by authors], defined doses, different infusion concentrations) and subgroups primiparae and multiparae'.

1. Pain intensity and/or satisfaction with pain relief (as defined by authors).

2. Breastfeeding exclusive* or full** or partial*** (time points specified by authors)

3. Method of delivery (unassisted vaginal birth, assisted vaginal birth, caesarean section)

4. Acidosis in neonate (as defined by cord blood arterial pH less than 7.15)

5. Admission to special care baby unit/neonatal intensive care unit (as defined by authors)

6. Poor infant outcomes at long-term follow-up (as defined by authors e.g. disability, brachial plexus damage, seizures)

We will use the *GRADEpro* Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Our statistician (Alan Watkins (AW)) will identify appropriate methods for variables to be analysed. Random-effects methods will be selected, where appropriate.

Dichotomous data

Data will be dichotomised wherever possible, using established and validated criteria, for example, pain scales with gradations of none-mild-moderate-severe or visual analogue scales with specified cut points (Moore 2013).

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

For rare adverse events, including many adverse events, the Peto odds ratio will be appropriate. Variables where some studies report zero counts will be considered appropriately, with further checks on calculations.

Sensitivity analyses will be undertaken dichotomising data to different drug aliquot masses.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the

standardised mean difference to combine trials that measure the same outcome, but use different methods. We shall follow our statistician's (AW's) advice regarding transformation of skewed data.

Unit of analysis issues

Cluster-randomised trials

We do not anticipate identifying many cluster-randomised trials. However, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Not applicable.

Other unit of analysis issues

More than two treatment groups

Where possible, groups will be combined to allow pairwise comparisons. This will be facilitated by alignment with definitions of high and low doses within the trials identified. Data will be explored using a series of drug mass aliquots as cut points: 50, 100, 150, 200, 300 mcg (Beilin 2005; COMET 2001; Radzinski 2003). Trial arms will be aligned with drug aliquot cut points, for example ≤ 50 mcg versus > 50 mcg. The analysis will be repeated with drug concentrations, and volumes infused.

We shall seek advice on meta-regression for multiple treatment meta-analysis as a supplementary analysis, if we locate sufficient data.

Twins and multiple pregnancies

We propose to use the same unit of analysis procedures as the included trials, and report this. To remove multiple pregnancies from the data would break the trial's randomisation. (See [Types of participants](#), above)

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using [Sensitivity analysis](#).

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

We shall undertake sensitivity analyses excluding participants not receiving their allocated treatment (*per protocol* analysis) and excluding trials where outcomes have more than 20% missing data.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a τ^2 is greater than zero, or there is a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Where outcomes are not reported, we shall contact trial authors to seek missing outcome data.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity

is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of τ^2 and I^2 .

We shall explore the relationship between opioid doses and concentrations and pain scores, using meta-regression, if sufficient data are available. However, pain scores from different settings may not be comparable. Therefore, we shall explore the relationship between the differences in change in pain scores, or the proportions with satisfactory pain relief, and the differences in doses between the trial arms. If we locate sufficient studies, we shall explore a meta-regression of the differences between doses and pain relief, both in absolute terms and as ratios. We shall explore predictor variables, such as trial sample size, any other analgesia co-administered. We propose to do this as a secondary analysis. We shall repeat the main analysis including trials where doses of non-opioid analgesia were not identical across the trial arms. (AW will guide the analysis.)

We shall justify our decisions on clinical and statistical grounds (Riley 2011).

Subgroup analysis and investigation of heterogeneity

Heterogeneity may arise from differences in co-administered analgesia in different trials. If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses (listed below). We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it. The number and nature of trials identified will determine the feasibility of subgroup analyses.

We shall analyse individual drugs separately and together. Doses and concentrations vary with each drug. All opioids administered by the epidural route will be analysed separately, and then in combination using recognised dose equivalence charts. Equivalence data are available for fentanyl, alfentanil, sufentanil, morphine, diamorphine and other opioids from manufacturers' literature and Internet sources. We shall use the fentanyl: sufentanil potency ratio of 6.3:1, derived in labouring women, as described by Herman 1998 in their study of 100 women (who were not followed through to the birth and therefore would not meet the criteria for inclusion in this review).

We think we have identified all relevant subgroups *a priori*. *Post hoc* subgroup analyses will be undertaken, if needed, and interpreted cautiously.

We plan to carry out the following subgroup analyses if data are available.

1. Primiparous *versus* multiparous parturients
2. Term *versus* preterm birth (as defined by authors)
3. Continuous support in labour *versus* no continuous support
4. Administration of epidural analgesia containing opioids before *versus* after 4 cm dilatation of cervix
5. Spontaneous labour *versus* induced labour
6. Trials with less than 48 hours *versus* those with 48 or more hours follow-up
7. Individual drugs *versus* all other drugs in combination
8. Resource-poor *versus* resource-rich settings
9. Trials undertaken before *versus* after publication of COMET 2001. Before 2001 *versus* 2002 and after, excluding 2001 trials
10. Trials administering high (more than 1.25%) *versus* low doses ($\leq 1.25\%$) of local anaesthetic epidural infusions (COMET 2001)
11. Regimens relying on solely bolus *versus* bolus/infusion administration, because transfer to the circulation may be more complete with infusions (Ginosar 2003)

Subgroup analysis will be restricted to the review's primary outcomes.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

Sensitivity analyses will be undertaken:

1. where there is risk of bias associated with the quality of some of the included trials, in 1 or more of the following criteria based on 'Assessment of risk of bias' (Higgins 2011):

- i) allocation concealment unclear;
- ii) participants unblinded;
- iii) outcome assessors unblinded for subjective outcomes, such as pain or satisfaction;
- iv) data analysts unblinded (Personnel are unlikely to be blinded as to the regimen administered);
- v) $\geq 20\%$ missing data;
- vi) registered protocol unavailable or mismatch between outcomes in registered protocol and reports of the trial;
- vii) imbalance between trial arms in analgesia before or after labour.

2. excluding *per protocol* and 'as treated' analyses in turn;
3. to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity;
4. dichotomising data to different drug mass aliquots;
5. excluding trials wholly or partially funded by pharmaceutical companies;
6. excluding cluster-randomised controlled trials.

Sensitivity analysis will be restricted to the review's primary outcomes.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Databases search strategy

SEARCH STRATEGIES (Bibliographic Databases)

PubMed (NLM) [1946-]

Search filter (lines 43 to 52) is adapted from Cochrane Handbook (Higgins 2011) - Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format.

1. birth[tiab] OR childbirth[tiab]
2. labor[tiab] OR labour[tiab]
3. parturient*[tiab] OR parturition[tiab]
4. intrapartum[tiab]
5. "Delivery, Obstetric"[mesh:noexp]
6. "Labor, Obstetric"[mh]
7. "Labor, Induced"[mh]
8. "Vaginal Birth after Cesarean"[mh]
9. "Labor Pain"[mh]
10. "Parturition"[mh]
11. "Obstetric Labor Complications"[mh]
12. OR /1-11
13. epidural*[tiab] OR neuraxial[tiab]
14. "Anesthesia, Epidural"[mesh:noexp]
15. "Analgesia, Epidural"[mh]
16. OR /13-15
17. alfentanil OR alfentanil
18. buprenorphine
19. butorphanol
20. diamorphine
21. fentanil OR fentanyl
22. heroin
23. hydromorphone
24. meperidine
25. methadone
26. morphine
27. nalbuphine
28. opiate*
29. opioid OR opioids
30. oxycodone
31. pentazocine
32. pethidine
33. sufentanil OR sulfentanil OR sufentanyl OR sulfentanyl
34. tramadol
35. "Analgesics, Opioid"[mh]
36. OR / 17-35
37. "Dose-Response Relationship, Drug"[mh]
38. "administration and dosage" [Subheading]
39. posolog*[tiab]
40. dose[tiab] OR doses[tiab] OR dosage*[tiab] OR dosing[tiab]
41. ED95[tiab] OR ED50[tiab]
42. OR/ 37-41
43. randomized controlled trial[pt]
44. controlled clinical trial[pt]

45. randomized[tiab]
46. groups[tiab]
47. clinical trials as topic[mesh:noexp]
48. randomly[tiab]
49. trial[ti]
50. OR / 43-49
51. AND / 12, 16, 36, 42, 50
52. animals[mh] NOT humans[mh]
53. (51 NOT 52)

SCOPUS (Elsevier) [coverage primarily 1960-]

KEY - searches author keywords, Emtree, Mesh and other index terms included in record

1. KEY("Delivery,Obstetric")
2. TITLE-ABS-KEY(labor OR labour)
3. TITLE-ABS-KEY(birth OR childbirth)
4. TITLE-ABS-KEY(parturient* OR parturition)
5. TITLE-ABS-KEY(intrapartum)
6. OR / 1-5
7. TITLE-ABS-KEY(neuraxial)
8. TITLE-ABS-KEY(epidural*)
9. OR / 8-9
10. TITLE-ABS-KEY(nalbuphine)
11. TITLE-ABS-KEY(morphine)
12. TITLE-ABS-KEY(methadone)
13. TITLE-ABS-KEY(meperidine)
14. TITLE-ABS-KEY(hydromorphone)
15. TITLE-ABS-KEY(heroin)
16. TITLE-ABS-KEY(fentan?l)
17. TITLE-ABS-KEY(buprenorphine)
18. TITLE-ABS-KEY(sufentan?l OR sulfentan?l)
19. TITLE-ABS-KEY(opioid*)
20. TITLE-ABS-KEY(diamorphine)
21. TITLE-ABS-KEY(butorphanol)
22. TITLE-ABS-KEY(alfentan?l)
23. TITLE-ABS-KEY("narcotic analgesic agent*")
24. TITLE-ABS-KEY(tramadol)
25. TITLE-ABS-KEY(pethidine)
26. TITLE-ABS-KEY(pentazocine)
27. TITLE-ABS-KEY(oxycodone)
28. TITLE-ABS-KEY(opiate*)
29. OR / 10-28
30. TITLE-ABS-KEY(ed95 OR ed50 OR dose OR doses OR dosage* OR dosing OR posolog*)
31. TITLE-ABS-KEY(RANDOM* W/5 STUDY)
32. ABS(groups)
33. TITLE-ABS-KEY(RANDOM* W/5 GROUP*)
34. KEY("comparative study")
35. KEY("controlled study")
36. KEY("Prospective Study")
37. TITLE-ABS-KEY(Random* W/2 assign*)
38. TITLE-ABS-KEY(Random* W/4 allocat*)
39. TITLE-ABS-KEY(Random* W/4 trial*)
40. TITLE-ABS-KEY(clinical PRE/2 trial* OR controlled PRE/2 trial*)
41. TITLE-ABS-KEY(randomi?ation)

42. TITLE-ABS-KEY(randomly)
43. TITLE-ABS-KEY ("triple blind*" OR tripleblind* OR "treble blind*" OR trebleblind*)
44. TITLE-ABS-KEY ("double blind*" OR doubleblind*)
45. TITLE-ABS-KEY ("single blind*" OR singleblind*)
46. KEY("random allocation")
47. TITLE-ABS-KEY(Randomi?ed)
48. KEY("Controlled trial*")
49. KEY("Clinical trial*")
50. OR / 31-49
51. AND / 6, 9, 29, 30, 50

Web of Science (Thomson Reuters - ISI)

Science Citation Index Expanded (SCI-EXPANDED) --1970-present

Social Sciences Citation Index (SSCI) --1970-present

Conference Proceedings Citation Index- Science (CPCI-S) --1990-present

TS - searches abstract, title and keywords

1. TS= (alfentan?l OR buprenorphine OR Butorphanol OR diamorphine OR fentan?l)
2. TS= (heroin OR hydromorphone OR meperidine OR methadone OR morphine OR nalbuphine OR opiate* OR opioid* OR oxycodone)
3. TS= (pentazocine OR pethidine OR sufentan?l OR sulfentan?l OR tramadol)
4. TS=("narcotic analgesic*")
5. OR / 1 - 4
6. TS=(birth OR childbirth OR parturient* OR parturition OR intrapartum)
7. TS=((labo\$r NEAR/1 pain) OR (labo\$r NEAR/1 analgesia) OR (labo\$r NEAR/2 an\$esthesia) OR (labo\$r NEAR/1 onset) OR (labo\$r NEAR/2 stage) OR (obstetric NEAR/1 delivery))
8. OR / 6 - 7
9. TS= (epidural OR neuraxial)
10. TS=(ed95 OR ed50 OR dose OR doses OR dosage* OR dosing OR posolog*)
11. TS= (single-blind* OR double-blind* OR treble-blind* OR triple-blind* OR singleblind* OR doubleblind* OR trebleblind* OR tripleblind*) OR TS= (random*) OR TS= (controlled NEAR/2 trial*) OR TS= (clinical NEAR/2 trial*) OR TS= (RCT) OR TS= ("comparative study" OR "major clinical study" OR "multicenter study") OR TS= (groups)
12. AND / 5,8,9,10,11

MATERNITY & INFANT CARE DATABASE (OvidSP) [1971 -]

.af. = all fields .de. = descriptors .hw.= heading words .ab. = abstract .ti. = title

1. (parturition or parturient\$ or birth or childbirth or labor or labour or delivery or intrapartum).af.
2. (epidural or neuraxial).af.
3. (alfentanyl or alfentanil or Buprenorphine or Butorphanol or methadone or tramadol or diamorphine or Fentanyl or fentanil or heroin or Hydromorphone or meperidine or Morphine or Nalbuphine or opiate\$ or opioid\$ or oxycodone or Pentazocine or pethidine or Sulfentanil or Sufentanil or sulfentanil or sufentanil).af.
4. Narcotics.de.
5. OR / 3 - 4
6. (dose or doses or dosing or dosage\$ or posolog\$ or ED95 or ED50).af.
7. AND / 1, 2, 5, 6
8. Randomised controlled trials.de.
9. Quantitative research.de.
10. (random\$ or groups or single-blind\$ or double-blind\$ or triple-blind\$ or treble-blind\$ or singleblind\$ or doubleblind\$ or tripleblind\$ or trebleblind\$).af.
11. (trial\$ or stud\$).ab,hw,ti.
12. OR / 8 - 11
13. AND 7, 12

CINAHL Plus with Full Text (Ebsco) [1937 -]

MH = Cinahl Subject Heading. MW= Word in Subject Heading.

Where no fields specified the term(s) are searched in the following fields: Title, Abstract and MW

1. TI birth OR AB birth
2. parturition OR parturient*
3. (MH "Labor+")
4. TI childbirth OR AB childbirth OR (MH "Childbirth+")
5. TI(labor OR labour) OR AB(labor OR labour) OR (MH "Labor Complications+")
6. (MH "Delivery+")
7. (MH "Intrapartum Care+") OR TI intrapartum OR AB intrapartum
8. OR / 1 - 7
9. epidural OR neuraxial
10. (alfentanil OR alfentanil OR buprenorphine OR butorphanol OR diamorphine OR fentanil OR heroin OR hydromorphone OR meperidine OR methadone OR morphine OR nalbuphine OR opiate* OR opioid* OR oxycodone OR pentazocine OR pethidine OR sufentanil OR sulfentanil OR tramadol)
11. (MH "Analgesics, Opioid+")
12. OR / 10 - 11
13. dose OR doses OR dosage* OR dosing OR posolog* OR ED95 OR ED50
14. (MH "Clinical Trials+")
15. (PT Clinical trial)
16. single blind* or double blind* or treble blind* or triple blind* or singleblind* or doubleblind* or trebleblind* or tripleblind*
17. MH "Quantitative Studies"
18. MH "Random Sample"
19. TI randomi?ed or AB randomi?ed
20. TI randomly or AB randomly
21. TI trial* OR (TI study OR AB study)
22. AB groups OR TI groups
23. PT randomized controlled trial
24. OR /14 - 23
25. AND / 24, 13, 12, 9, 8
26. (MH "Animals+") NOT (MH "Humans+")
27. 25 NOT 26

Appendix 2. Clinical trials search strategy

SEARCH STRATEGIES for Clinical Trials Registers

ClinicalTrials.gov

((epidural OR neuraxial) AND (labor OR labour OR parturients OR parturition OR birth OR childbirth OR delivery))

ISRCTN Registry

((epidural OR neuraxial) AND (labor OR labour OR parturients OR parturition OR birth OR childbirth OR delivery))

International Federation of Pharmaceutical Manufacturers and Associations [IFPMA]

Epidural [including synonyms] AND labor pain [including synonyms] AND opioids [including synonyms]

WHO International Clinical Trials Registry Platform Search Portal [WHO ICTRP]

Advanced search.

Intervention: epidural OR neuraxial

Condition: labour OR labor OR birth OR childbirth OR delivery

Recruitment status: All

CONTRIBUTIONS OF AUTHORS

Sue Jordan drafted the protocol, with input from Clare Boucher, Fiona Murphy, Alan Watkins, Lucy de Lloyd and Stuart Davies. All authors commented on the draft protocol.

DECLARATIONS OF INTEREST

Susan Jordan - was awarded a small grant was by the Children and Young People's Research Network of the NISCHR (National Institute for Social Care and Health Research) Cymru to cover the costs of administrators' and librarians' time and the cost of meetings. Sue also receives royalties in relation to the following textbook: Jordan S. 2010 'Pharmacology for midwives: the Evidence Base for Safe Practice' Palgrave/ Macmillan, Basingstoke 2nd edition ISBN-13: 978-0-230-21558-0 pp. 486

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Clare Boucher - co-applicant on a small grant from the Children and Young People's Research Network of the NISCHR (National Institute for Social Care and Health Research) Cymru to cover the costs of administrators' and librarians' time and the cost of meetings.

Stuart Davies - none known

Amy Brown - none known

Alan Watkins - none known

Lucy J de Lloyd - none known

Margery Morgan - none known

Gareth Morgan - is a member of the Welsh Government Life Sciences Sector (LSS) Ministerial Advisory Panel and has received per diem and travel expenses for LSS advisory work one day per month.

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